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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/139,425	08/25/98	ESMON C	OMRF-171

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1636	7
DATE MAILED:	10/21/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/139,425	Applicant(s) Esmon et al.
	Examiner WILLIAM SANDALS	Group Art Unit 1636

☒ Responsive to communication(s) filed on *Aug 16, 1999*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-25* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☒ Claim(s) *13-15 and 20-25* is/are allowed.

☒ Claim(s) *1-12 and 16-19* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *6*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Drawings

1. The drawings as submitted on August 9, 1999, have been approved by the draftsman.

Response to Arguments

2. Applicant's amendments to the specification in Paper No. 5, filed August 16, 1999 has overcome the rejection of claims , 4-5, 12, 14 and 17 under 35 USC 112, second paragraph in the previous office action, and the rejections are withdrawn.

3. Applicant's amendments to the specification in Paper No. 5, filed August 16, 1999 has overcome the rejection of claims 1-25 under 35 USC 112, first paragraph in the previous office action, and the rejections are withdrawn. (with exception to claims 5-7 and 16-19 as indicated in item #6 below)

4. Applicant's arguments filed August 16, 1999 regarding the rejection of claims 13-15, 19-20, 22 and 24-25 under 35 USC 102(b) and 102(e) have been fully considered and are found persuasive, and the rejection is withdrawn.

5. Applicant's arguments filed August 16, 1999 regarding the rejection of claims 13-15, 19-20, 22 and 24-45 under 35 USC 103(a) have been fully considered and are found persuasive and the rejection is withdrawn.

6. Applicant's arguments filed August 16, 1999 regarding the rejection of claims 5-6 and 16-18 under 35 USC 112, first paragraph have been fully considered but they are not persuasive. The response to the arguments is contained in the rejection repeated below.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 5-7 and 16-19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method of selectively delivering genes to a large vessel endothelial cell nucleus by binding a conjugate to an endothelial protein C receptor (EPCR). While applicants have shown the binding of a conjugate to an endothelial protein C receptor (EPCR) *in vitro*, they have not demonstrated any *in vivo* delivering of a gene to an endothelial cell, which constitutes a method of gene therapy. In order to do so, undue experimentation is required. Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors. Many of these factors have been summarized in *In re Wands*, 858 F.2d 731, USPQ2d 1400 (Fed. Cir. 1988).

The Wands factors as they apply to the instant claimed invention are as follows:

a- The quantity of experimentation necessary to reduce the instant claimed invention to practice would involve delivering a gene to an endothelial cell for gene therapy.

b- Only prophetic guidance and no examples of delivering a gene to an endothelial cell *in vivo* have been provided.

c- The nature of the invention is complex. Gene therapy is a new and developing art as recited in Marshall in the section titled "The trouble with vectors", and at page 1054, column 3, and at page 1055, column 3. The problems of gene delivery, gene targeting to reach the intended host cell, and then to reach the intracellular target are not yet solved, as taught in Verma et al. (see especially page 239, column 3, the box titled "What makes an ideal vector?" and page 242).

d- The prior art taught by Orkin et al. (see especially the section on "Gene transfer and expression" and "Gene therapy in man status of the field") described many problems in the developing field of gene therapy. Recited problems include: lack of efficacy, adverse short term effects and limited clinical experience, the inability to extrapolate experimental results and unreliability of animal models. Problems with the vector include: host immune response to the vector and the expressed product, difficulty of targeting the vector to the desired site, transient expression of the gene of interest and low efficiency of delivery of the vector to the targeted site.

e- The state of the art as taught by Verma et al., which states "the problems - such as the lack of efficient delivery systems, lack of sustained expression, and host immune reactions - remain formidable problems" and Anderson, W. F. (see page 25, top of column 1), which states

"[e]xcept for anecdotal reports of individual patients being helped, there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease".

f- Therefore, given the analysis above, it must be considered that the skilled artisan would have needed to have practiced considerable non-routine, trial and error experimentation to enable the full scope of the claims.

Response to Arguments

Applicants have argued in Paper No. 5, that the argument above pertains to viral vectors. In as much as the references discuss viral vectors, those sections which are specific to the use of viral vectors for delivery of a nucleic acid to a cell clearly do not apply to the instant claimed invention. However, the bulk of the content of the references discusses the application of gene therapy, which does apply.

The statement in Anderson, WF, makes it clear that the state of the art in gene therapy, or delivery of nucleic acids for therapeutic purposes, is still a poorly understood art, and the references provided by applicant, while encouraging, do not overcome the problems facing practitioners in the gene therapy art, and make it clear that applicants must provide detailed teachings on how to make and use such an invention. Since these teachings are not presented in the instant claims and specification, the instant claimed invention is not enabled.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1, 3, 8 and 10-12 are rejected under 35 U.S.C. 102(b) as being anticipated by WO9605303.

The claims are drawn to a method of administering a conjugate of an agent which binds selectively to an endothelial protein C receptor (EPCR) where the agent is conjugated to a molecule to be delivered to a large vessel endothelial cell. The agent may be activated protein C. The molecule to be delivered may a drug or a diagnostic agent.

(WO9605303) taught (see especially the abstract and pages 15-16, 18-26, the Figures and the Claims) a method of administering a conjugate of an agent which binds selectively to an endothelial protein C receptor (EPCR) where the agent is conjugated to a molecule to be delivered to a large vessel endothelial cell. The agent may activated protein C. The molecule to be delivered was a diagnostic agent. There may be a coupling means which binds the agent and the molecule to be delivered, which may be a positively charged polymer or biotin-streptavidin.

The preamble of the claim states that the method is for the delivering of molecules to the nucleus of the endothelium of the large vessels. The steps of the claimed invention are identical to the steps taught by the instant references, which is a method of administering a conjugate of an agent which binds selectively to an endothelial protein C receptor (EPCR) where the agent is

conjugated to a molecule to be delivered to a large vessel endothelial cell. The result of the method, the delivery of the conjugate to the nucleus, must follow as a consequence of the method.

11. (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

12. Claims 1, 3, 8 and 10-12 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat No. 5,695,993 or US Pat No. 5,852,171.

The claims are drawn to a method of administering a conjugate of an agent which binds selectively to an endothelial protein C receptor (EPCR) where the agent is conjugated to a molecule to be delivered to a large vessel endothelial cell. The agent may be activated protein C. The molecule to be delivered may a drug or a diagnostic agent. delivered, which may be a positively charged polymer or biotin-streptavidin.

US Pat No. 5,695,993 (see especially the abstract, the summary and columns 5-16) or US Pat No. 5,852,171 (see especially the abstract, the summary and columns 5-16) taught a method of administering a conjugate of an agent which binds selectively to an endothelial protein C receptor (EPCR) where the agent is conjugated to a molecule to be delivered to a large vessel endothelial cell. The agent was protein C or activated protein C. The molecule to be delivered was a diagnostic agent. There may be a coupling means which binds the agent and the molecule to be delivered, which may be a positively charged polymer or biotin-streptavidin.

The preamble of the claim states that the method is for the delivering of molecules to the nucleus of the endothelium of the large vessels. The steps of the claimed invention are identical to the steps taught by the instant references, which is a method of administering a conjugate of an agent which binds selectively to an endothelial protein C receptor (EPCR) where the agent is conjugated to a molecule to be delivered to a large vessel endothelial cell. The result of the method, the delivery of the conjugate to the nucleus, must follow as a consequence of the method.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 1-4 and 8-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO96/05303, or US Pat No. 5,695,993 or 5,852,171 in view of Jans et al.

The claims are drawn to a method of administering a conjugate of an agent which binds selectively to an endothelial protein C receptor (EPCR) where the agent is conjugated to a molecule to be delivered to a large vessel endothelial cell. The agent may be protein C, activated protein C or an antibody (which may be chimeric). The molecule to be delivered may be a

protein, a drug or a diagnostic agent, and where the molecule to be delivered may be a transcription factor.

WO9605303 (see especially the abstract and pages 15-16, 18-26, the Figures and the Claims), or US Pat No. 5,695,993 (see especially the abstract, the summary and columns 5-16) or US Pat No. 5,852,171 (see especially the abstract, the summary and columns 5-16) taught a conjugate of an agent which bound selectively to an endothelial protein C receptor (EPCR) and a molecule to be delivered to a large vessel endothelial cell. The agent may be protein C, activated protein C or an antibody (which may be chimeric). The molecule to be delivered was a diagnostic agent. There was a coupling means which bound the agent and the molecule to be delivered, which may be a positively charged polymer or biotin-streptavidin.

WO96/05303, or US Pat No. 5,695,993 or 5,852,171 did not teach that the molecule to be delivered may be a transcription factor.

Jans et al. taught (see the entire article) that the delivery of a molecule into a cell via receptor-mediated endocytosis is well known in the art, and transcription factors are taught to promote nuclear transport through nuclear localization signals within the transcription factors.

The preamble of the claim states that the method is for the delivering of molecules to the nucleus of the endothelium of the large vessels. The steps of the claimed invention are identical to the steps taught by the instant references, which is a method of administering a conjugate of an agent which binds selectively to an endothelial protein C receptor (EPCR) where the agent is conjugated to a molecule to be delivered to a large vessel endothelial cell. The result of the

method, the delivery of the conjugate to the nucleus, must follow as a consequence of the method.

It would have been obvious to one of skill in the art at the time of the instant invention to combine the teachings of WO96/05303, or US Pat No. 5,695,993 or US Pat No. 5,852,171 with Jans et al. to produce the instant claimed invention because WO96/05303, or US Pat No. 5,695,993 or US Pat No. 5,852,171 taught a conjugate of an agent binding selectively to an endothelial protein C receptor (EPCR) and a molecule to be delivered to a large vessel endothelial cell where the agent was an antibody (which may be chimeric). The delivery of conjugates to cells via a cell surface receptor is well known in the art, and the use of any receptor to bind a conjugate for delivery into a cell is an obvious choice within the purview of the ordinary skilled artisan. Jans et al. taught a conjugate which binds to a cell surface receptor which facilitates the delivery of the conjugate to the cell. The instant claimed receptor, EPCR, being one of many obvious receptors for the delivery of conjugates to a cell by way of a well known method of delivery as taught in WO96/05303, or US Pat No. 5,695,993 or US Pat No. 5,852,171 and Jans et al. The delivery of a transcription factor as taught by Jans et al. is a well known use of receptors for delivery of conjugates into a cell.

One of skill in the art would have been motivated at the time of the instant invention to combine the teachings of WO96/05303, or US Pat No. 5,695,993 or US Pat No. 5,852,171 with Jans et al. to produce the instant claimed invention because WO96/05303, or US Pat No. 5,695,993 or US Pat No. 5,852,171 taught a conjugate of an agent binding selectively to an

endothelial protein C receptor (EPCR) and a molecule to be delivered to a large vessel endothelial cell where the agent was an antibody (which may be chimeric). The delivery of conjugates to cells via a cell surface receptor is well known in the art, and the use of any receptor to bind a conjugate for delivery into a cell is an obvious choice within the purview of the ordinary skilled artisan. The delivery of conjugates to cells via a cell surface receptor is well known in the art as stated in Jans et al. at page 404, column 1 "endocytosis brings activated receptor molecules inside the cell, permitting their subsequent transport to specific intracellular compartments". At page 409, Jans et al. state "NLS-dependent targeting, subsequent to binding and internalization at the plasma membrane, of ligand receptor complexes to the nucleus where they may participate directly or indirectly in regulating gene transcription represents a signaling mechanism that guarantees the specificity of response to a particular ligand." The instant claimed receptor, EPCR being one of many obvious receptors for the delivery of conjugates to a cell by way of a well known method of delivery as taught in WO96/05303, or US Pat No. 5,695,993 or US Pat No. 5,852,171 with Jans et al. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of WO96/05303, or US Pat No. 5,695,993 or US Pat No. 5,852,171 with Jans et al.

Allowable Subject Matter

15. Claims 13-15 and 20-25 are allowed.

Conclusion

16. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Friday from 8:30 AM to 5:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott can be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Receptionist, whose telephone number is (703) 308-0196.

William Sandals, Ph.D.
Examiner
October 14, 1999

JOHN S. BRUSCA, PH.D
PRIMARY EXAMINER